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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,561	03/19/2002	Jerry M Collins	31978-178825	6698

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EXAMINER	
JONES, DAMERON LEVEST	

ART UNIT	PAPER NUMBER
1616	7

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/088,561	COLLINS ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- Th MAILING DATE of this communicati n appears on the cover sheet with the c rrespondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *25-27 and 30-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☒ Claim(s) *28 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

APPLICANT'S INVENTION

1. Applicant's invention is directed to compounds, uses thereof, and methods of making those compounds wherein a drug is labeled with a positron emitter.

Note: Claims 1-40 are pending.

RESPONSE TO APPLICANT'S ELECTION

2. Applicant's election with traverse of Group I, claims 1-24, 28, and 29, in Paper No. 6, filed 5/28/03, is acknowledged. The traversal is on the grounds that (1) a lack of unity was never asserted during the international stage and is now improper; and (2) there is unity of invention because the single general inventive concept is the use of the radiolabeled probes that comprise specific anti-cancer agents having a label incorporated into the structure without adding additional structural features, and the use of those probes for PET scanning. (3) Applicant asserts that while the method claims (claims 1-9) are applicable to a wide range of chemical compounds, the application is not so broad as to require the Examiner to search all possible drugs since the application is specifically directed to compounds which are labeled anti-cancer drugs. (4) The Examiner has not properly set forth the reasoning for asserting a lack of unity of invention. (5) The Examiner should have made an election of species rather than restricted the instant application. This is found non-persuasive for the reasons set forth below. First, Applicant is respectfully reminded that while a lack of unity was not made during the international stage, it does not necessarily mean that the application did not lack unity. Secondly, for clarification of the record, Applicant is reminded that under

PCT Rule 13.1 applications should relate to one invention or to a group of invention so linked as to form a single general inventive concept. Where a group of inventions is claimed, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features as set forth under PCT 13.2. The expression 'special technical features' is interpreted as a technical feature that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The instant application is directed to multiple products, processes of manufacture, and uses of the products (e.g., see for example, claims 1, 2, 13, 20, 28, 29, 30, 31, 32, 35, 37, 39, and 40). The compounds, for example, encompassed in claim 20 are structurally different from those of claims 32 and 39. Furthermore, even though Applicant asserts that the invention concept is the use of radiolabeled anti-caner agents for PET imaging, it should be noted that, for example, [18F]fluorotamoxifen is an agent that has been evaluated using PET scanning in patients with breast cancer (see Inoue et al, Clinical Imaging, 1997, 21:332-336, document is listed on the information disclosure statement filed 3/19/02). Srinivasa et al (Bioorganic & Medicinal Chemistry, 1998, 6:2193-2204, listed on Applicant's IDS), discloses [14C]-labeled paclitaxel derivatives. Hendrikse et al (Cancer Research, May 1999, 59:2411-2416, listed on Applicant's IDS) disclose [11C]-daunorubicin and [11C]verapamil accumulation in tumors. Thus, Hendrikse et al concluded that PET and radiolabeled P-gp substrates are useful as a clinical tool to select patients who might benefit form the addition of a P-gp modulator to MDR drugs. Kangas et al (Pharmacology & Toxicology, 1989, 64:373-

377, listed on Applicant's IDS) disclose a study wherein the evaluation of tumor imaging of [11C]-toremifene was conducted using PET. Accordingly, the unity of invention is considered to be lacking and restriction in accordance with the rules of unity of invention are considered to be proper. Furthermore, as set forth by the unity of invention rules for multiple inventions, Applicant is entitled to a product, a process specifically adapted for that product, and a use of that product. Hence, the restriction requirement is proper since the groups encompass a product, uses of that product, methods of making that product. The restriction requirement is still deemed proper and is therefore made FINAL.

Note: Applicant's invention was not extended beyond elected Group I.

WITHDRAWN CLAIMS

3. Claims 25-27 and 30-40 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention/species.

103 REJECTIONS

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Page et al (US Patent No. 5,981,564) in view of Li et al (US Patent No. 6,441,025) in further view of Schirbel (Berichhte des Forschungszentrums Julich (1998), 3602, pp. 1-110).

Page et al disclose paclitaxel derivatives having an increased solubility in water (see entire document, especially, abstract). The derivatives may be used to detect apoptosis of cells, for in vivo treatment or prophylaxis of cancer by administering a therapeutically effective amount of the derivative to a patient in need, or for in vivo labeling of tubulin (column 2, lines 44-68). Page discloses that the paclitaxel derivative may be labeled with a marker such as a fluorescent marker or a radioactive marker (column 3, lines 1-13 and 48-51). The water-soluble paclitaxel derivatives have Formula I as set forth in column 3, lines 17-40. It should be noted that when the variables R and R' are hydrogen, the compound is paclitaxel. However, Page et al fail to (a) disclose specifically disclose carbon-11 labeled paclitaxel even though the document discloses that paclitaxel may be labeled ; (b) specifically state that the paclitaxel derivatives may be imaged by positron emission tomography; (c) disclose that 11C-paclitaxel may be used in combination with other drugs or with modulators; and (d) disclose all the possible types of cancers/tumors that may be treated with paclitaxel derivatives.

Li et al disclose water-soluble compositions of paclitaxel formed by conjugating the paclitaxel to a water-soluble polymer such as polyglutamic acid, polyaspartic acid, or polylysine. The compositions are useful for the treatment of tumors (see entire

document, especially, abstract). In addition, Li et al disclose that their compositions provide water soluble taxoids that overcome the drawbacks associated with the insolubility of the drugs themselves and provide the advantages of improved efficacy and controlled release so that tumors may be eradicated after a single intravenous administration (column 3, lines 22-28). The methods of Li et al may be used to make water-soluble polymer conjugates of other therapeutic agents, contrast agents, and drugs (e.g., paclitaxel). The conjugates may be administered in conjunction with other drugs including anti-tumor/anti-cancer drugs. The water-soluble paclitaxel may, in certain types of treatment, be combined with a platinum drug, an anti-tumor agent (e.g., doxorubicin or daunorubicin), other drugs that are used in combination with paclitaxel, or combined with external or internal irradiation (column 3, lines 49-59). The compositions of Li et al may contain a radionuclide and be used as an anti-tumor agent or drug. The pharmaceutica composition may include a therapeutic amount of a chelated radioactive isotope (column 6, lines 14-18). The paclitaxel compositions may be used to treat cancer by administering a pharmaceutically acceptable composition to a subject in an amount effective to treat the tumor. The compositions of Li et al are effective against any type of cancer including breast cancer, ovarian cancer, malignant melanoma, lung cancer, head cancer, and neck cancer. Also, Li et al disclose that the use of the term 'treating' cancer as set forth in their invention is understood as meaning any medical management of a subject having a tumor (column 6, lines 46-65). Radiolabeled paclitaxel is useful in imaging tumors. One is able to determine whether a paclitaxel will be taken up by a particular tumor by imaging techniques such as positron

emission tomography or single photon emission computer tomography. This determination may then be used to predict the efficacy of an anti-cancer treatment (column 14, lines 19-30).

Schirbel discloses that carbon-11 is a positron emission tomography radioindicator that offers unique possibility of authentic labeling of molecules for non-invasive and quantitative determination of physiological functions (see entire document, especially, page 1, 'Synthesis of n.c.a. PET-radiotracers with carbon-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Page et al using the teachings of Schirbel and Li et al and generate compounds and methods of use thereof comprising 11C-paclitaxel for the reasons set forth below. (1) Page et al discloses that their paclitaxel derivatives may be radiolabeled. (2) Li et al discloses paclitaxel conjugates that may also be radiolabeled and used for various imaging techniques including positron emission tomography. (3) Schirbel discloses that carbon-11 offers unique possibilities of authentic labeling of molecules as radioindicators for non-invasive and quantitative determination of physiological functions via positron emission tomography. (4) Li et al disclose that paclitaxel conjugates are effective against any type of cancer/tumor including breast cancer, ovarian cancer, malignant melanoma, lung cancer, head and neck cancer, gastric cancer, prostate cancer, colon cancer, leukemia, and Kaposi's Sarcoma (column 6, lines 46-57).

(5) Also, it should be noted that Li et al disclose that 'modulators', water soluble polymers, may be conjugated to paclitaxel to overcome the drawbacks associated with

the insolubility of the drugs themselves and to provide the advantages of improved efficacy and controlled release so that tumors may be eradicated after a single administration of the drug (column 3, lines 22-28). (6) Furthermore, Li et al disclose that it is known in the art to use anti-tumor/anti-cancer drugs in combination. For example, paclitaxel conjugates may be used in combination with other drugs such as doxorubicin or combined with external or internal irradiation (column 3, lines 49-59).

Since each of the references cited disclose paclitaxel, the documents may be considered to be within the same field of endeavor. Hence, the references are combinable.

CLAIM OBJECTIONS

6. Claims 28 and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Note: The claims are distinguished over the prior art of record because the prior art neither anticipates nor renders obvious the method of synthesizing 11C-paclitaxel as set forth in claims 28 and 29.

OBJECTION TO THE SPECIFICATION

7. The disclosure is objected to because of the following informalities: the continuing data is missing from the specification. In particular, Applicant is respectfully requested to incorporate the continuing data on page 1, first paragraph. Specifically,

the instant should incorporate "This application is a 371 of PCT/US00/25833, filed 9/21/00 which claims benefit of provisional application 60/155,061, filed 9/21/99".

Appropriate correction is required.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

August 7, 2003